ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–15
https://doi.org/10.1093/eurheartj/ehad197

SPECIAL ARTICLE
Dyslipidaemias

2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance

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Received 15 August 2022; revised 22 December 2022; accepted 16 March 2023

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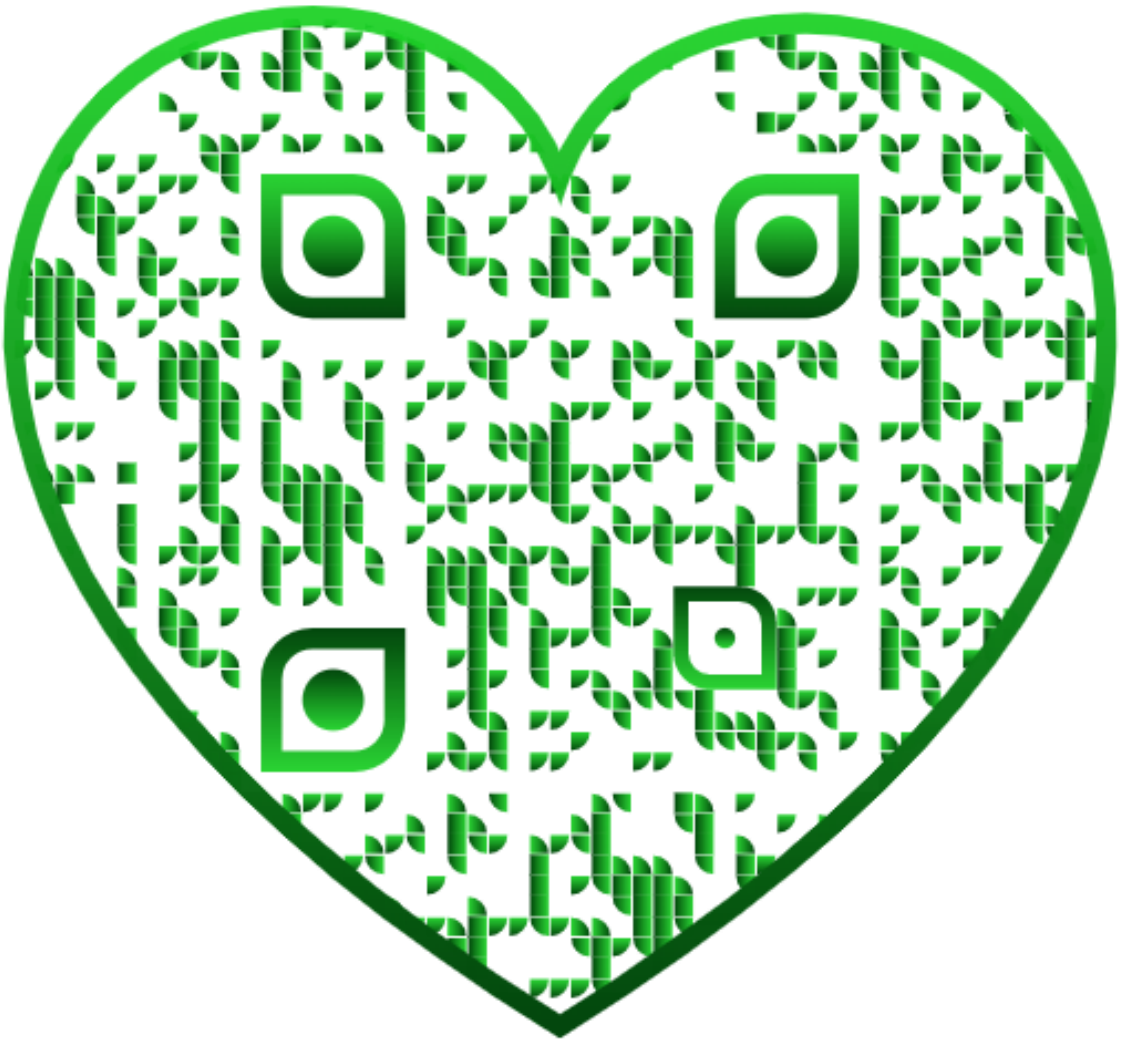
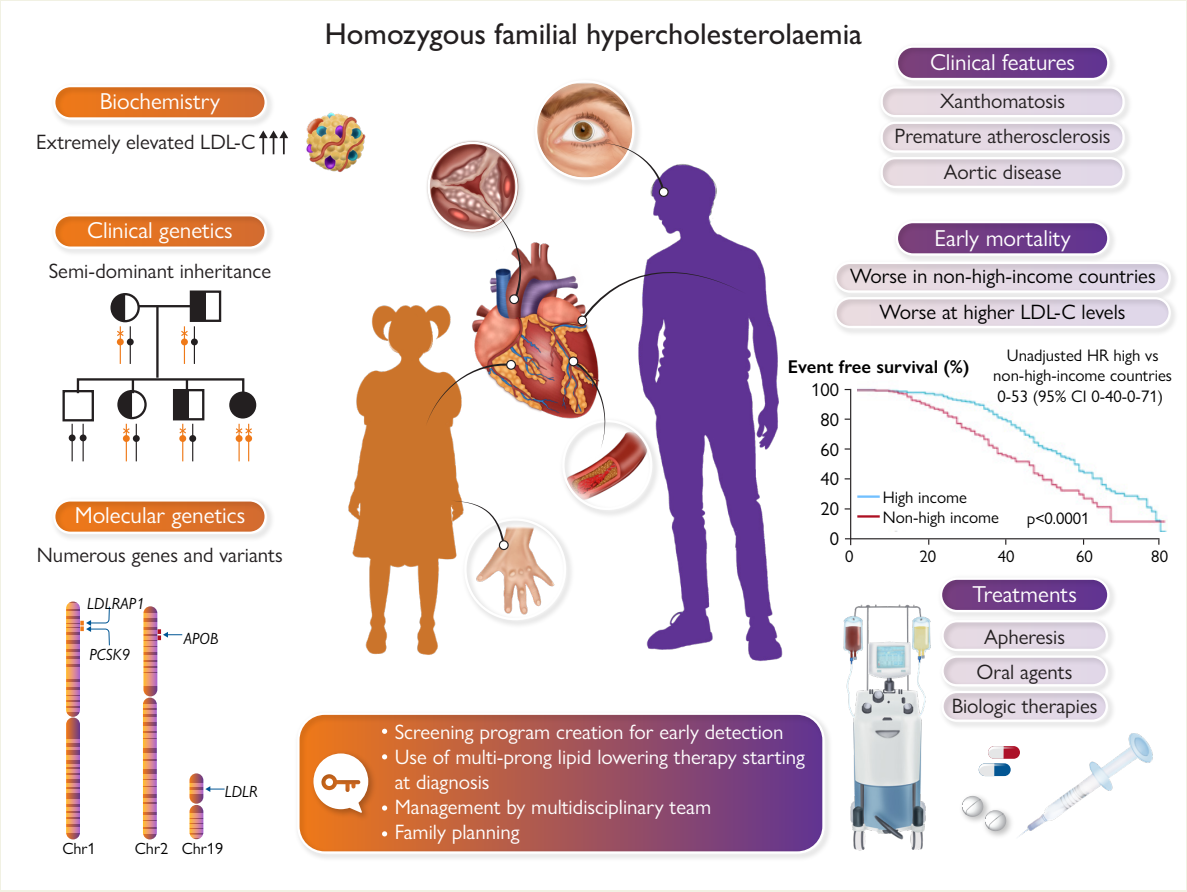


Graphical Abstract



Homozygous familial hypercholesterolaemia is a rare autosomal semi-dominant disease affecting males and females equally, characterized by markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) from conception and accelerated atherosclerotic cardiovascular disease, often resulting in early death. Homozygous familial hypercholesterolaemia is diagnosed late and undertreated; both established and novel therapies offer hope to patients, but treatment inequity exacerbates poorer outcomes in less affluent countries.[12] *APOB*, apolipoprotein B gene; CI, confidence interval; HR, hazard ratio; *LDLR*, low-density lipoprotein receptor gene; *LDLRAP1*, low-density lipoprotein adaptor protein 1 gene; *PCSK9*, proprotein conertase subtilisin/kexin type 9 gene.

Abstract

This 2023 statement updates clinical guidance for homozygous familial hypercholesterolaemia (HoFH), explains the genetic complexity, and provides pragmatic recommendations to address inequities in HoFH care worldwide. Key strengths include updated criteria for the clinical diagnosis of HoFH and the recommendation to prioritize phenotypic features over genotype. Thus, a low-density lipoprotein cholesterol (LDL-C) >10 mmol/L (>400 mg/dL) is suggestive of HoFH and warrants further evaluation. The statement also provides state-of-the art discussion and guidance to clinicians for interpreting the results of genetic testing and for family planning and pregnancy. Therapeutic decisions are based on the LDL-C level. Combination LDL-C-lowering therapy—both pharmacologic intervention and lipoprotein apheresis (LA)—is foundational. Addition of novel, efficacious therapies (i.e. inhibitors of proprotein convertase subtilisin/kexin type 9, followed by evinacumab and/or lomitapide) offers potential to attain LDL-C goal or reduce the need for LA. To improve HoFH care around the world, the statement recommends the creation of national screening programmes, education to improve awareness, and management guidelines that account for the local realities of care, including access to specialist centres, treatments, and cost. This updated statement provides guidance that is crucial to early diagnosis, better care, and improved cardiovascular health for patients with HoFH worldwide.

Keywords Homozygous familial hypercholesterolaemia • Clinical guidance • Diagnosis • Genetics • Treatment • Women

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Introduction

In 2014, the European Atherosclerosis Society (EAS) statement on homozygous familial hypercholesterolaemia (HoFH)[1] focused attention on this rare and life-threatening disease, characterized by markedly elevated plasma low-density lipoprotein cholesterol (LDL-C) levels from birth and accelerated atherosclerotic cardiovascular disease (ASCVD). At that time, HoFH had limited therapeutic options. Expert-led call-to-action statements and guidance[2–9] catalysed enormous progress, particularly in understanding the genetic complexity of HoFH and in developing new treatments. However, persistent questions regarding screening, diagnosis, and management require a new consensus statement (*Box 1*).

Box 1 What is new in this EAS Consensus Statement on HoFH?

- Updated diagnostic criteria
- New insights into the genetics of HoFH
- Updated recommendations on screening strategies for early identification
- Updated recommendations for cardiac work-up at diagnosis and follow-up
- Updated treatment algorithm incorporating novel treatments
- Updated guidance on family planning for HoFH women of childbearing potential and heterozygous FH parents

Underdiagnosis and undertreatment of HoFH are major issues impacting HoFH care. Recent estimates indicate that ~30 000 people worldwide have HoFH (*Figure 1*),[10,11] but <5% are identified.[12] Inadequate awareness and ascertainment efforts, and a disconnect between clinical diagnosis and interpretation of genetic results by health providers and payers contribute to underdiagnosis. HoFH care is suboptimal, as shown by the HoFH International Clinical Collaborators (HICC) global registry,[12] a clinician-founded initiative supported by the EAS including over 750 individuals from 38 countries (both high- and non-high-income regions). Diagnosis is made too late (median age 12 years), with ~10% of patients showing clinical coronary atherosclerosis or aortic valve disease, and only 5% attain LDL-C goals.[12] Treatment inequity is a major issue impacting patient cardiovascular health in less affluent countries.[12] Urgent action is clearly needed to (i) improve awareness, and (ii) implement pragmatic clinical guidance for HoFH care, recognizing practical issues in different world regions. This second EAS statement updates evidence and addresses practical constraints impacting equity in care. How to balance advances in scientific knowledge with the realities of care globally is key to improving HoFH diagnosis and management.

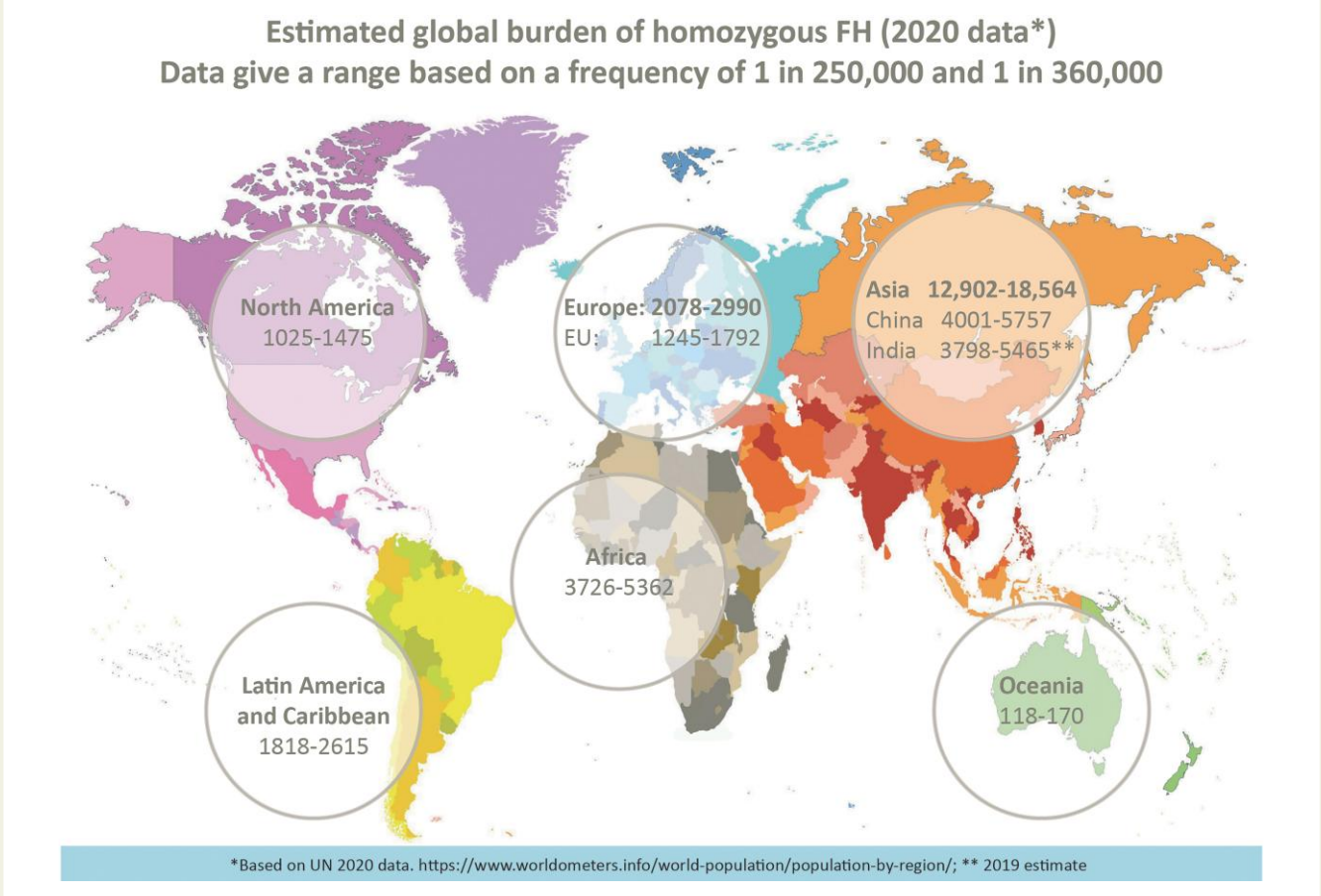

Figure 1 Estimated global prevalence of homozygous familial hypercholesterolaemia by United Nations world region, based on 2020 population data and estimates of homozygous familial hypercholesterolaemia prevalence ranging from 1:250 000 to 1:360 000.[10,11]

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Box 2 Updated criteria for the diagnosis of homozygous familial hypercholesterolaemia

Clinical criteria

- LDL-C criteria:
  Untreated LDL-C >10 mmol/L (>~400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis.
- Additional criteria:
  Cutaneous or tendon xanthomas before age of 10 years and/or
  untreated elevated LDL-C levels consistent with heterozygous FH in both parents*
  *In digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH.

Genetic criteria

- Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* genes or ≥2 such variants at different loci (*Box 3*); for abbreviations for genetic nomenclature see below.

ABCG5, *ABCG8*: Genes encoding ATP-binding cassette subfamily G members 5 and 8
APOB: Gene encoding apolipoprotein B
LDLR: Gene encoding the low-density lipoprotein receptor
LDLRAP1: Gene encoding low-density lipoprotein receptor adaptor protein 1
LIPA: Gene encoding lysosomal acid lipase
PCSK9: Gene encoding proprotein convertase subtilisin/kexin type 9 protein (PCSK9)

Diagnosis of homozygous familial hypercholesterolaemia

Clinical criteria

Plasma LDL-C is the critical discriminator for clinical diagnosis of HoFH. The 2014 EAS consensus statement recommended LDL-C diagnostic criteria of >13 mmol/L (>500 mg/dL) for untreated patients or >8 mmol/L (>300 mg/dL) for patients treated with conventional therapy (i.e. statin plus ezetimibe), together with evidence of cutaneous or tendon xanthomas before 10 years, or untreated elevated LDL-C levels consistent with heterozygous FH in both parents.[1] However, LDL-C criteria are not the sole guide to diagnosis, given the genetic complexity of HoFH (see below) and variability in LDL-C levels and clinical phenotype; indeed, LDL-C levels <13 mmol/L were reported in several cohorts of genetically confirmed HoFH.[12–14] Therefore, this panel proposes that HoFH should be suspected if untreated LDL-C levels are >10 mmol/L (>~400 mg/dL), requiring further evaluation, including a detailed medical and family history and/or genetic testing (*Box 2*). The multiplicity of lipid-lowering treatments that these patients typically receive means that historic cut-offs for treated LDL-C are probably obsolete.

Clinicians should exclude other conditions associated with elevated LDL-C levels before making a diagnosis of HoFH (*Figure 2A*). These include sitosterolaemia (or 'phytosterolaemia'), caused by bi-allelic rare pathogenic variants in two ATP-binding cassette transporter genes, *ABCG5* and/or *ABCG8* (or at least one such variant in each gene), with elevated LDL-C levels that respond well to dietary recommendations, ezetimibe and/or resins,[15–17] and lysosomal acid lipase deficiency (i.e. cholesterol ester storage disease), caused by bi-allelic pathogenic variants in the *LIPA* gene, and for which enzyme replacement treatment is available.[18] Patients with cerebrotendinous xanthomatosis may have xanthomas resembling HoFH but plasma cholesterol levels are normal to mildly elevated (with elevated cholestanol levels) associated with neurological, cognitive, and ophthalmic symptoms.[19,20]

Key recommendation: An untreated LDL-C level >10 mmol/L (>~400 mg/dL) suggests HoFH and requires further evaluation.

Genetic criteria and interpreting genetic test results

The term 'HoFH' dates from the pre-genomic era when scientists and clinicians envisioned a simple scenario in which the identical pathogenic variant was present on both alleles of an affected individual, as sometimes observed in consanguineous matings. Pathogenic variants were mainly in three main genes, *LDLR* (loss-of-function), *APOB* (receptor-binding defective), and *PCSK9* (gain-of-function), accounting for 85%–90%, 5%–10%, and 1%–3%, respectively, of all variants causing semi-dominant FH.[21] More recently, a rare autosomal recessive form of FH [autosomal recessive hypercholesterolaemia (ARH)] accounting for <1% of cases was identified, caused by bi-allelic loss-of-function variants in *LDLRAP1* (see abbreviations in *Box 2*); heterozygotes are true 'carriers': with normal LDL-C levels.[22]

As an autosomal semi-dominant condition,[23] individuals with one copy of a pathogenic DNA variant—i.e. mono-allelic or heterozygous FH (HeFH)—express an abnormal biochemical phenotype, sometimes with characteristic clinical features. Individuals with bi-allelic pathogenic variants (one pathogenic variant inherited from each parent, each on a different chromosome, i.e. genotypic HoFH) have more extreme LDL-C deviation and more severe clinical features from a younger age. Mono-allelic and bi-allelic forms—i.e. HeFH and HoFH—have a prevalence of ~1 in 250–300[10,11] and ~1 in 250 000–360 000, respectively.[24] In some populations, such as French Canadians, Afrikaners in South Africa, or Christian Lebanese, HoFH prevalence may be at least 10-fold higher due to founder effects.[10,11,24]

The molecular complexity initially described in the 2014 consensus statement[1] was reaffirmed by next-generation DNA sequencing (NGS). Most patients have two different pathogenic variants either in the same (i.e. monogenic) or two different (i.e. digenic) causative genes. Permutations (shown in *Table 1*) include bi-allelic variants (identical or different) from a single gene, as well as different bi-allelic variants from two different genes (digenic inheritance). This resulted in confusing descriptions such as 'compound heterozygous' or 'double heterozygous' form of HoFH. To avoid misinterpretation, the panel suggests retaining the operational term 'phenotypic HoFH' as a useful clinical shorthand in the absence of a genetic diagnosis, while acknowledging the underlying

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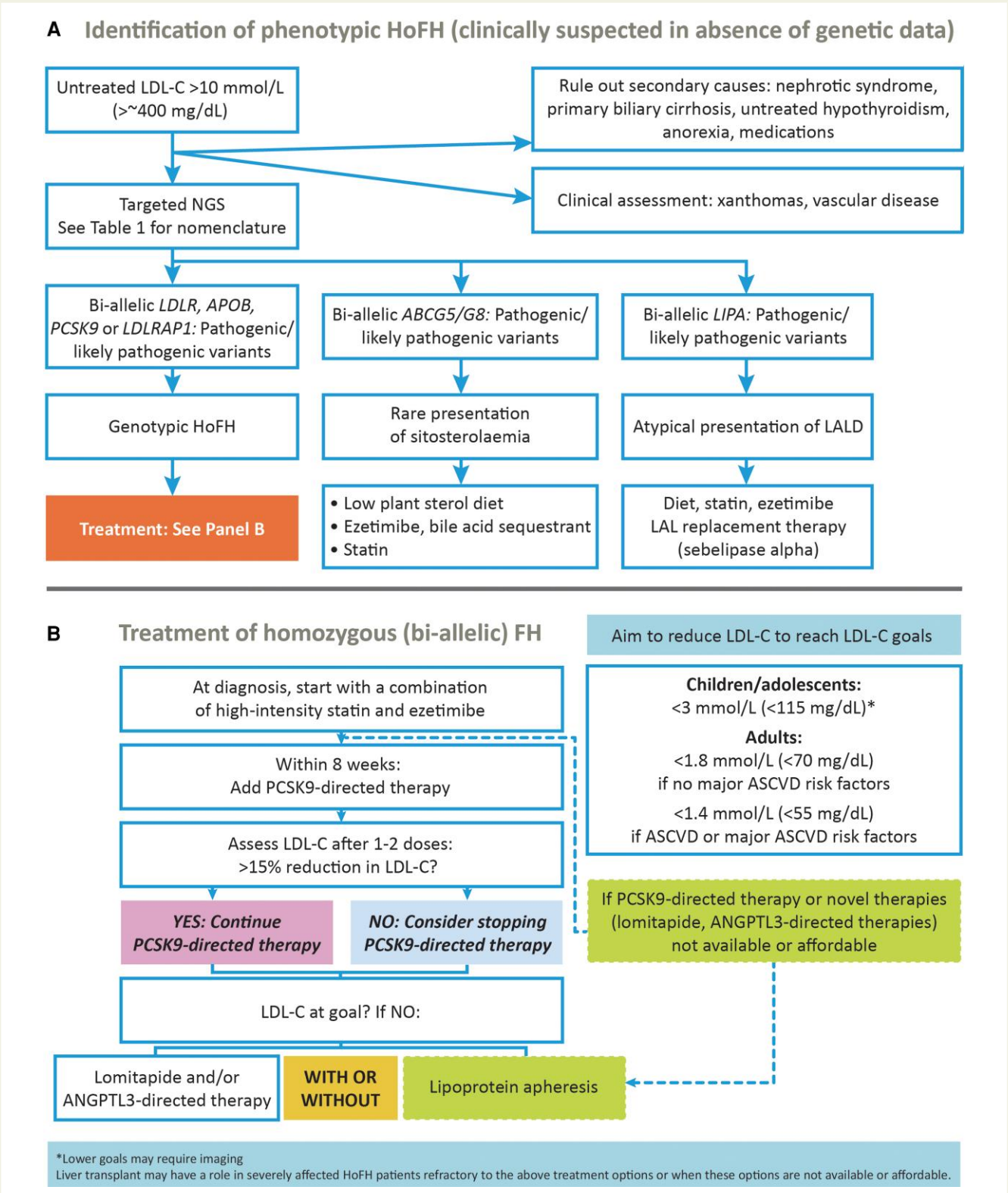
A Identification of phenotypic HoFH (clinically suspected in absence of genetic data)
Untreated LDL-C >10 mmol/L (>~400 mg/dL)
Rule out secondary causes: nephrotic syndrome, primary biliary cirrhosis, untreated hypothyroidism, anorexia, medications
Clinical assessment: xanthomas, vascular disease
Targeted NGS See Table 1 for nomenclature
Bi-allelic LDLR, APOB, PCSK9 or LDLRAP1: Pathogenic/ likely pathogenic variants
Bi-allelic ABCG5/G8: Pathogenic/ likely pathogenic variants
Bi-allelic LIPA: Pathogenic/ likely pathogenic variants
Genotypic HoFH
Rare presentation of sitosterolaemia
Atypical presentation of LALD
Treatment: See Panel B
• Low plant sterol diet
• Ezetimibe, bile acid sequestrant
• Statin
Diet, statin, ezetimibe
LAL replacement therapy (sebelipase alpha)
B Treatment of homozygous (bi-allelic) FH
Aim to reduce LDL-C to reach LDL-C goals
At diagnosis, start with a combination of high-intensity statin and ezetimibe
Children/adolescents:
<3 mmol/L (<115 mg/dL)*
Adults:
<1.8 mmol/L (<70 mg/dL)
if no major ASCVD risk factors
<1.4 mmol/L (<55 mg/dL)
if ASCVD or major ASCVD risk factors
Within 8 weeks:
Add PCSK9-directed therapy
Assess LDL-C after 1-2 doses:
>15% reduction in LDL-C?
YES: Continue PCSK9-directed therapy
NO: Consider stopping PCSK9-directed therapy
If PCSK9-directed therapy or novel therapies (lomitapide, ANGPTL3-directed therapies) not available or affordable
LDL-C at goal? If NO:
Lomitapide and/or ANGPTL3-directed therapy
WITH OR WITHOUT
Lipoprotein apheresis
*Lower goals may require imaging
Liver transplant may have a role in severely affected HoFH patients refractory to the above treatment options or when these options are not available or affordable.

Figure 2 Identification and treatment of homozygous familial hypercholesterolaemia. (*A*) Algorithm for identification of phenotypic homozygous familial hypercholesterolaemia when clinically suspected in the absence of genetic data. (*B*) Treatment algorithm for homozygous familial hypercholesterolaemia (bi-allelic). ANGPTL3, angiopoietin-like 3; ASCVD, atherosclerotic cardiovascular disease; LALD, lysosomal acid lipase deficiency; LDL-C, low-density lipoprotein cholesterol; NGS, next-generation DNA sequencing; PCSK9, proprotein convertase subtilisin/kexin type 9.

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Table 1 Modern genetic nomenclature for the clinical homozygous familial hypercholesterolaemia phenotype

Traditional clinical terminology	Precise nomenclature based on genetics	Comments
Homozygous familial hypercholesterolaemia (HoFH): *an umbrella term that encompasses a spectrum of genetic diagnoses*	1. Bi-allelic semi-dominant hypercholesterolaemia: monogenic (single gene)	'Semi-dominant' indicates that mono-allelic (i.e. heterozygote) relatives have a less severe phenotype
	(a) defined by causative genes:	
	• *LDLR*-related	Accounts for 85%–90% of all variants
	• *APOB*-related	Accounts for 5%–10% of all variants
	• *PCSK9*-related	Accounts for 1%–3% of all variants
	(b) defined by nature of variants:	
	· 2 copies of the identical variant	Formerly called 'true' or 'simple' HoFH
	· 1 copy each of 2 different variants	Formerly called 'compound heterozygous FH'
	2. Bi-allelic semi-dominant hypercholesterolaemia: digenic (two different causal genes)	'Semi-dominant' indicates that mono-allelic (i.e. heterozygote) relatives have a less severe phenotype
	(a) defined by causative genes:	
	• *LDLR*-related plus *APOB*-related	Accounts for 90%–95% of cases with digenic variants
	• *LDLR*-related plus *PCSK9*-related	Accounts for 2%–5% of cases with digenic variants
	• *APOB*-related plus *PCSK9*-related	Accounts for <2% of cases with digenic variants
	(b) defined by nature of variants:	
	· 1 copy each of 2 different variants	Formerly called 'double heterozygous FH'
	3. Bi-allelic recessive hypercholesterolaemia: single gene	Heterozygous parents are true carriers with normal clinical and biochemical phenotypes
	(a) defined by causative gene:	
	• *LDLRAP1*-related	Accounts for all patients with this subtype;<1% of all cases of 'HoFH'.
	(b) defined by nature of variants:	
	· 2 copies of the identical variant	Formerly called 'true' or 'simple' ARH
	· 1 copy each of 2 different variants	Formerly called 'compound heterozygous' ARH

Box 3 Sources of genetic complexity of phenotypic homozygous FH

Genetic heterogeneity
- *LDLR* gene loss-of-function variants: >3000 reported, accounting for 85%–90% of cases
- *APOB* gene-receptor-binding-impaired variants accounting for 5%–10% of cases
- *PCSK9* gene gain-of-function variants accounting for 1%–3% of cases
- *LDLRAP1* gene loss-of-function variants accounting for <1% of cases

Variable inheritance patterns
- Semi-dominant (i.e. *LDLR*, *APOB*, and *PCSK9* genes)
- True autosomal recessive (i.e. *LDLRAP1* gene)

Variant types
- Usually interpreted as a 'null' variant of *LDLR* (≤ 2% functional activity)
  - Copy number variants (i.e. large insertion or deletion of genetic material)
  - Nonsense variant resulting in premature termination
    - small insertion or deletion that shifts the reading frame
    - single nucleotide variant introducing a stop codon
  - Splicing variant
  - A few missense variants (defined below) are proven experimentally to be 'null'
- Usually interpreted as a 'defective' variant of *LDLR* (2%–70% functional activity)
  - Typically, a missense (i.e. single nucleotide) variant altering a single amino acid residue

See abbreviations in *Box 2* and Berberich and Hegele (2019).[21]

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Box 4 Benefits and limitations of genetic testing in HoFH

Benefits
- Permits a definitive diagnosis
- Allows for objective visualization of the underlying genetic complexity
- Enables access to appropriate current and emerging therapies and clinical trials
- Can predict disease severity and treatment response in populations or cohorts, within limits
- Can rule out similar conditions that require other treatments (e.g. sitosterolaemia)
- Triggers cascade screening to find new patients with HeFH or phenotypic HoFH
- Can facilitate prenatal genetic counselling
- Knowledge of a definitive genetic basis can promote adherence to optimal therapy

Limitations
- Accessibility and cost
- Predicting individual phenotype and clinical response from genotype is not straightforward
- Pathogenicity for many detected DNA variants cannot be definitively established
- Some patients with phenotypic HoFH have only one or even no pathogenic variant detected
- Some patients with bi-allelic pathogenic variants express HeFH but not HoFH phenotypically
- The healthcare provider must be cautious not to overinterpret genetic results
- Professional pre- and post-test genetic counselling is desirable but usually unavailable

genetic complexity, as reported by genetic diagnostic laboratories (*Box 3*, *Table 1*). This more precise genetic terminology supersedes traditional terms such as 'simple' or 'true homozygote', 'compound heterozygote' and 'double heterozygote'.

Targeted NGS diagnostic panels predominantly used today will eventually be replaced by high-pass exome or genome methods.[21] Results from all methods are reported similarly but interpretation can present challenges for the care provider.[25] Genetic reports describe variants as benign/likely benign, variant of uncertain or unknown significance (VUS), or pathogenic/likely pathogenic.[26] Ascribing pathogenicity to DNA variants is a challenge faced by the entire genetics field. This panel recommends that clinicians only consider variants reported as 'pathogenic/likely pathogenic' according to criteria from the American College of Medical Genetics and Genomics modified for FH when communicating a confirmed genetic diagnosis to patients.[25,26] VUS are not diagnostic, but potentially could be reclassified as pathogenic in the future.

Key recommendation: Consider only variants reported as 'pathogenic/likely pathogenic' according to recognized criteria as a confirmed genetic diagnosis of HoFH.

Variants in *LDLR* are often classified as 'null' (≤2% activity) or 'receptor defective' (2%–70% activity) based on their predicted impact on receptor function. Yet only ∼10% of all variants have been directly functionally tested; instead, most have been classified based on predictive algorithms, particularly missense variants.[25] There are general patterns of genotype-phenotype correlation, with *LDLR* null variants having the most extreme LDL-C deviations and most blunted response to pharmacologic interventions.[27] However, the genotype cannot definitively predict the precise phenotypic expression in an individual patient.

On balance, the benefits outweigh the limitations of genetic testing in HoFH (*Box 4*), with increased certainty of diagnosis and access to, use of, and compliance with appropriate treatment. For example, genetic testing occasionally reveals causal variants in genes that normally cause non-FH dyslipidaemias such as *ABCG5* or *ABCG8* in sitosterolaemia, with distinct treatment implications, i.e. elimination of dietary sterols and use of ezetimibe rather than statins plus apheresis (*Figure 2A*).[18] However, genetic results can be potentially misunderstood or miscommunicated.[28] A few patients with phenotypic HoFH have only one identified pathogenic variant because of technical reasons, interactions with undiscovered causal genes, or an unmeasured background polygenic effect, although the latter is currently not felt to be an important genetic mechanism underlying phenotypic HoFH.[29] Furthermore, NGS has identified some individuals with phenotypic HeFH and an appropriate response to statins, who have two pathogenic variants on opposite chromosomes that would be expected to cause phenotypic HoFH.[30,31] In cases of discordance, this panel recommends that a phenotypic diagnosis, HoFH or HeFH, takes priority over the genetic results. Patients and families with genetic results that are either difficult to understand or complex should be referred to a genetic counsellor or clinician with extensive experience in human genetics and lipidology.[32]

Screening recommendations: key to early identification of homozygous familial hypercholesterolaemia

Early detection of HoFH is essential, but in practice is too late, as shown by the HICC registry.[12] Lack of awareness about HoFH and poor guideline implementation are important barriers. Current guidelines recommend screening in children at ≤2 years if there is a positive family history of premature ASCVD or hypercholesterolaemia, and universal cholesterol screening at ages varying from 5 to 11 years.[33–35] These guidelines are hardly followed, emphasizing the need for improved implementation.[36]

This panel strongly recommends (i) screening for HoFH whenever suspected clinically and/or with premature ASCVD; (ii) expansion of paediatric guidelines to include newborn lipid screening when both parents are known to have HeFH or hypercholesterolaemia without a confirmed diagnosis of HeFH, or in regions with a strong founder effect; and (iii) creation of national screening programmes in countries where these are lacking. This panel joins FH advocacy groups worldwide in calling for paediatric universal FH screening, taking into consideration specific conditions, needs and resources of individual countries, to improve identification of FH, including HoFH.[7,8,37,38]

Education programmes to increase awareness among health providers likely to have first contact with possible patients with HoFH due to signs such as xanthomas[1] is another priority to reduce time to diagnosis. Collaboration between paediatricians, primary healthcare providers, lipid specialists, cardiologists, and geneticists is highly desired. Use

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Box 5 Cardiovascular imaging in HoFH management

- Polyvascular subclinical atherosclerosis may be present in coronary, femoral, and carotid vascular territories in HoFH. Where available and easily accessible, imaging is an important tool in HoFH management.
- Carotid plaque rather than increased carotid intima-medial thickness is a marker of early stage atherosclerosis. Quantitative carotid plaque measurement by three-dimensional ultrasound is a reliable measure of disease progression and response to therapy. High-resolution magnetic resonance imaging (MRI) has been shown to detect thrombosis and lipid-rich carotid plaques.
- Patients with HoFH should receive echocardiographic evaluation of the heart and aorta at baseline and annually thereafter. CT angiography should be performed at least once after age 3 as it also allows for differentiation of coronary ostial stenosis (which may be asymptomatic) and aortic stenosis. A stress electrocardiogram should only be performed after exclusion of coronary ostial or tight aortic stenosis.
- Follow-up CT angiography should be performed as clinically indicated. The follow-up interval in children depends on baseline disease, extent of LDL-C lowering, radiation risk, and cost. Radiation may be less of an issue with newer CT devices and imaging protocols. Early imaging can help to identify soft plaque to target for intervention and asymptomatic atherosclerosis.
- Coronary calcium scoring is less predictive in young patients since extensive calcification may not yet have developed in the plaques.
- Invasive coronary angiography is indicated in patients with symptoms and/or signs suggestive of ischaemia or valve malfunction.
- The atherosclerotic burden of the aorta can also be evaluated by MRI or transoesophageal echocardiography.
- Careful electrocardiographic or nuclear stress testing may be used to determine the presence of ischaemia. Coronary flow velocity reserve determined noninvasively with echocardiography has also been used to determine risk.

of electronic medical records and strategies to flag laboratory levels suggestive of HoFH with prompts to guidelines would increase awareness and link providers to regional specialist centres for shared management of patients with HoFH.

Finally, as HoFH is a disease of the family, identification of a patient with LDL-C levels compatible with phenotypic HoFH must prompt evaluation of lipids and medical history of family members via 'reverse cascade' testing.[39] Ideally, this is centrally co-ordinated and undertaken by staff skilled in genetic and family counselling. Although genetic testing may facilitate identification of family members with FH, screening of lipid levels is acceptable, especially with privacy concerns among probands or parents and limited access to testing. For the autosomal semi-dominant subtype of HoFH (i.e. pathogenic variants in *LDLR*, *PCSK9*, and *APOB* genes), parents are obligate heterozygotes for single copy pathogenic variants in the same or different genes and are therefore at risk for elevated LDL-C levels (frequently >95th percentile by country-specific age and gender criteria) and a family history of premature ASCVD (<55 years in men and <60 years in women among first-degree relatives). For ARH, however, LDL-C levels in parents are in the normal range.[18]

Key recommendations

- Paediatric guidelines should include newborn lipid screening when both parents are known to have HeFH or simply hypercholesterolaemia.
- The panel advocates for paediatric universal FH screening that will also improve the detection of HoFH.
- Education programmes are needed to increase awareness among all healthcare providers.

Management plan

Referral of the patient with HoFH to a specialist centre for appropriate LDL-lowering therapy and reverse cascade screening is essential (see Supplementary data online, *Table S1*). Initial laboratory analysis should be comprehensive and include lipoprotein(a) [Lp(a)], which enhances cardiovascular risk.[40] Whether elevated Lp(a) also predisposes to accelerated aortic valve stenosis in HoFH warrants further study.

Because most patients with HoFH are identified in childhood, paediatricians have a key role in the management plan, to implement lifestyle measures and treat other ASCVD-risk factors.[1] Cardiologists (paediatric or adult) are integral to the multidisciplinary management team. Initial assessment should include physical examination and auscultation,

Box 6 Treatment pathway for homozygous familial hypercholesterolaemia in childhood. Adapted from Reijman *et al.*[50]

- Initiate lifestyle changes, statins, and ezetimibe from diagnosis
- If LDL-C >8 mmol/L (300 mg/dL), consider lipoprotein apheresis (LA)
- If LDL-C >3 mmol/L (115 mg/dL), consider novel therapies if available and affordable
- If LA or novel therapies are not available, consider liver transplantation

particularly valuable where there is limited access to imaging. Accelerated atherosclerosis, typically affecting the aortic root and coronary ostia, is characteristic of HoFH,[1] and calcific valvular aortic disease has become very prevalent with increasing longevity.[41]

Given diagnostic delay and disease severity, detailed cardiovascular imaging at baseline is strongly advised where available (*Box 5*). An echocardiogram and low-dose computed tomography (CT) angiography are recommended to identify disease burden with special emphasis on high-risk lesions in the coronary ostia. Low-dose CT is preferable for detection of subclinical coronary and aortic root atherosclerosis[41] and may help to guide therapy, as valvular and supravalvular aortic diseases may progress even when LDL-C levels are reduced. Tendon imaging is not recommended as part of routine clinical assessment. Different imaging protocols are required in adults vs. children, both requiring defined referral pathways and involving multidisciplinary discussion.

Treatment and low-density lipoprotein cholesterol goals

Given their very high risk, the panel proposes the same LDL-C goals in HoFH as recommended by guidelines for high- and very high-risk patients (*Figure 2B*). Thus, in adult patients with HoFH (≥18 years), the LDL-C goal is <1.8 mmol/L (<70 mg/dL), and <1.4 mmol/L (<55 mg/dL) with additional ASCVD-risk factors (elevated Lp(a), diabetes mellitus) or established ASCVD.[42] In children and adolescents, an LDL-C goal of <3 mmol/L (<115 mg/dL) is recommended if treatment is initiated before 18 years and imaging assessment does not indicate ASCVD, with

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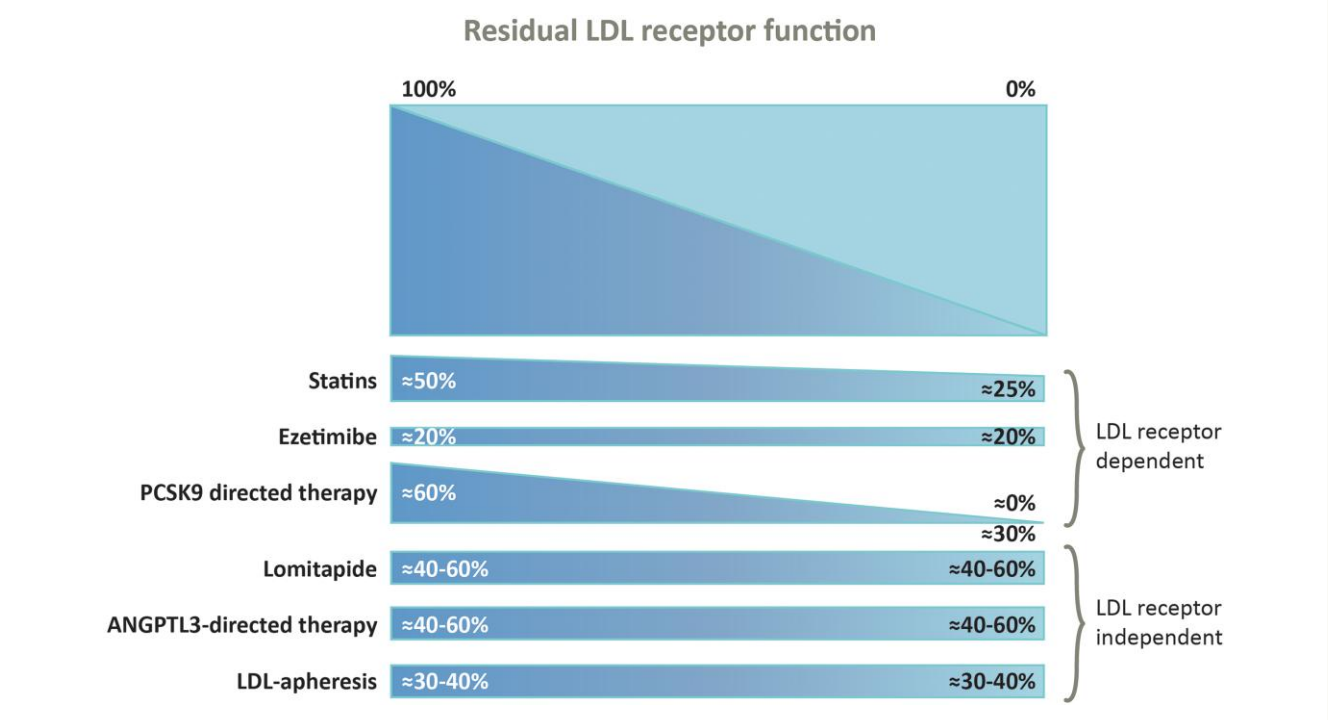

Figure 3 Response to statin, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is dependent on the degree of residual low-density lipoprotein receptor activity; however, for lomitapide, angiopoietin-like protein 3 (ANGPLT3)-directed therapy and lipoprotein apheresis, response is independent of low-density lipoprotein receptor function. Reproduced with permission from Mohamed *et al.*[44].

a lower goal in those with established ASCVD. The panel acknowledges that these goals are extrapolated from expert recommendations which have not been tested in clinical trials, and that attainment is challenging in real-world practice. In the HICC registry, only 12% of adult patients in high-income countries attained an LDL-C value <1.8 mmol/L.[12] The panel believes, however, that with continued progress in lipid-lowering treatment and access, goal attainment may improve in the future.

The LDL-C level (i.e. the phenotype) and not the presence of a genetic diagnosis drives therapeutic decisions (*Figure 2B*). Combination lipid-lowering therapy, both pharmacologic intervention and lipoprotein apheresis (LA), is foundational,[43] together with lifestyle measures (diet and smoking cessation). Treatment should be started as soon as possible, ideally at diagnosis. These recommendations also apply to children/adolescents, subject to local approval of pharmacotherapeutics, aiming to ensure adherence from an early age (*Box 6*).

Patients should start on a high-intensity statin and ezetimibe rather than statin monotherapy, but most will require additional therapies to attain goal. Within 8 weeks proprotein convertase subtilisin/kexin type 9 (PCSK9)-directed therapy should be considered where available. Response to these treatments is dependent on the degree of residual LDL receptor activity (*Figure 3*).[44] PCSK9 monoclonal antibody therapy (evolocumab or alirocumab at approved doses for HoFH) is effective in many patients with HoFH.[45–49] If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, clinicians should consider stopping this therapy. While the average LDL-C lowering of ~30% with PCSK9-directed therapy is likely to reduce the risk of ASCVD events, LDL-C levels will remain substantially above recommended goals for most patients. Subsequent options include LDL receptor–independent therapies and/or LA.

Novel therapies independent of residual low-density lipoprotein receptor function

Lomitapide is an oral inhibitor of the microsomal triglyceride transfer protein affecting the production of very low-density lipoproteins, the precursor of LDL.[51] In real-world practice, lomitapide added to standard of care treatment reduced plasma LDL-C levels by 60%, albeit with some variability in response,[52] and Lp(a) by ~15% at 26 weeks.[53] Lomitapide also provided better control of LDL-C than lipoprotein apheresis (LA).[54] Preliminary findings from the Pan-European Project in HoFH including 75 patients with HoFH showed that lomitapide treatment for up to 9 years (median 19 months) resulted in more than half attaining at least 50% reduction from baseline in LDL-C at last visit, with less need for apheresis in a substantial proportion of patients.[55] However, hepatic steatosis remains a concern and liver imaging has shown a moderate increase in hepatic fat with normal liver stiffness during longer term real-world treatment, consistent with clinical trial data.[56]

Another approach targets angiopoietin-like protein 3 (ANGPTL3), which modulates lipid-lipoprotein metabolism and has pleiotropic functions. The ANGPTL3 monoclonal antibody evinacumab is licensed for patients with HoFH aged at least 12 years, based on results from the ELIPSE HoFH trial, in which evinacumab (15 mg/kg intravenously every 4 weeks) reduced LDL-C by ~50% on top of maximally tolerated lipid-lowering therapy with or without LA, with comparable response during open-label treatment.[57] Long-term follow-up (median 53 weeks, maximum 132 weeks) showed durable and similar LDL-C lowering in adults and adolescents (43% and 52%, respectively).[58,59] Importantly, response to evinacumab did not depend on *LDLR* genotype and was similar in patients with bi-allelic null variants or with predicted residual LDL receptor function.[57]

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Data with these newer agents are, however, limited in children with HoFH. To address this, the panel strongly supports creation of a fast-tracked regulatory pathway for approval of novel treatments in young children with HoFH; e.g. evinacumab was recently approved for children aged 5–11 years by the US Food and Drug Administration. As most countries do not have access to these newer agents, and, where available, cost may limit their use, other approaches such LA are a viable alternative.

Lipoprotein apheresis

Lipoprotein apheresis is foundational in children and adults with HoFH, adjunctive to other lipid-lowering therapy,[60] and is therefore vital in countries without access to newer therapies. Limitations include variable access, cost, and a time-consuming procedure impacting patient's quality of life.[61] Treatment should be started as soon as possible, in children ideally by age 3 and not later than 8 years, depending on appropriate venous access. LA is usually performed fortnightly or even weekly. If not available, plasma exchange may be considered. Registry data provide strong evidence for the efficacy and clinical benefit of LA in adults, with resolution of clinical manifestations such as xanthomas and no major safety concerns to date.[62,63] Rebound effects are slower in HoFH than in HeFH (up to 30 days) with an average LDL-C reduction of 55%, as well as over 50% reduction in Lp(a) concentration.[64,65] The frequency or requirement for apheresis may be reduced with novel therapies such as lomitapide and evinacumab.

Liver transplantation

Liver transplantation may be an option for a small subset of patients with HoFH, particularly severely affected young children with bi-allelic null variants. It may be considered a last resort, despite maximal therapy, with (i) evidence of progression of coronary artery disease (CAD) and LDL-C levels >1.8 mmol/L (>70 mg/dL), or (ii) minimal or stable CAD but LDL-C >13 mmol/L (>500 mg/dL). Combined liver/heart transplantation may be indicated for rapidly progressive disease or extensive heart damage.[2,66] Multiple case reports demonstrate normalization of LDL-C levels within a few weeks after transplantation of a normal donor liver, persisting up to 28 years.[67–70] Effects on CAD are less well-documented, although regression has been reported,[68,71–73] and the effect on aortic stenosis is uncertain.[67,68,74] The benefits of liver transplantation need to be balanced against the risks, which include surgical complications, acute and chronic rejection of the donor liver, and side effects of immunosuppressive therapy, although these have decreased since first report in 1984 and will vary by institution.[2] Access to an experienced paediatric or adult liver transplant centre and lack of contraindications for transplant surgery and immunosuppressive regimens, including the possibility of poor compliance, are essential. This panel advocates for the creation of a global registry of patients with liver transplantation to facilitate more comprehensive assessment of this approach.

Emerging therapeutic approaches

Novel approaches to PCSK9 and ANGPTL3 blockade, including small interfering (si)RNA therapies, are in development. Advances in biotechnology offer the future possibility of liver-directed gene transfer and gene editing for HoFH.[75,76] Adeno-associated virus (AAV)-mediated gene transfer is a viable approach to long-term transgene expression in pre-clinical models of HoFH. A first-in-human phase 1/2 trial of an AAV-mediated human *LDLR* gene transfer in nine patients with HoFH was recently completed (NCT02651675).[75] In preclinical models, CRISPR (clustered regularly interspaced short palindromic repeats)-based gene editing has been successful in modifying both *ANGPTL3*[77] and *PCSK9*[78] and reducing LDL-C levels. A clinical trial with the first CRISPR PCSK9 treatment (VERVE-101) is ongoing in the UK and New Zealand and pending in the USA.[79] Although promising, these approaches require careful evaluation of intermediate and long-term safety and efficacy.

Key recommendations for managing HoFH

- Lipid-lowering treatment should start at diagnosis using multiple treatments and/or LA to reach LDL-C goal.
- A fast-track path for approval of novel treatments in children is needed to ensure their use from a young age, decreasing cumulative LDL-C exposure and improving outcomes.
- Gene therapy and CRISPR-based gene editing are promising approaches, but clinical trials are needed to evaluate efficacy and safety.
- Multidisciplinary management in specialist centres integrating imaging, treatment, and comprehensive support of these patients is needed.

Family planning and pregnancy

With advances in treatment, HoFH is becoming a more chronic, manageable disease, and individuals are increasingly likely to survive well into adulthood.[27] For HoFH women of child-bearing potential, timely discussion of adequate contraception is essential to prevent unplanned pregnancy. Safe methods with minimal risk of ASCVD are preferred, although the panel recognizes the need to respect personal preference in an informed context. Family planning discussions are essential to management in both men and women, incorporating a model of care with cholesterol testing of the partner and genetic counselling, as children will have obligate HeFH.

A multidisciplinary team and an integrated care approach before, during, and after pregnancy are particularly important for HoFH women. Cardiovascular evaluation is recommended before pregnancy for risk assessment, including echocardiographic assessment of the pressure gradient across the aortic valve and root, and if possible, CT coronary angiography to evaluate CAD. Female patients should be counselled that pregnancy is associated with an increased cardiovascular risk and is potentially life-threatening; those with established CAD and/or aortic valve pathology should be referred to a high-risk obstetric clinic. Serum LDL-C levels can increase by 25%–50% during the second and particularly the third trimester of pregnancy. Although the relative increases are similar in individuals with and without FH, the absolute increases are much greater in FH, especially HoFH.[80] An individual management plan is needed from the patient's first wish to conceive to resumption of lipid-lowering medication.

Treatment during pregnancy and lactation is challenging as most lipid-lowering drugs, including statins until recently, are contraindicated. Although bile sequestering resins such as colesevelam are not associated with an increased risk of congenital abnormalities, data in pregnancy are scarce, their tolerability may be poor, and efficacy limited. Thus, HoFH women should be offered weekly or fortnightly LA during pregnancy.[81,82] If unavailable, continuation of statin therapy or reintroduction of statin plus other lipid-lowering therapy from the second trimester onwards appears to be safe.[83] Indeed, following recent comprehensive review, the FDA recommended changes in statin contraindications for pregnant women, recognizing the favourable risk/benefit ratio in high-risk women such those with HoFH.[84] Reintroduction of lipid-lowering therapy should be postponed in lactating HoFH women due to possible transfer to the breast milk; if

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prolonged, discussion with the mother regarding the risks is needed. Finally, heterozygous parents of an HoFH child considering another child should receive additional counselling and care.

Key recommendations

- HoFH women should receive integrated care from a multidisciplinary team, including cardiovascular assessment, before, during, and after pregnancy.
- To minimize LDL-C exposure, LA should be offered during pregnancy, and statin plus other lipid-lowering therapy restarted from the second trimester.

Quality of life

Few studies have assessed the quality of life of individuals living with HoFH. A recent meta-analysis showed overall impairment in quality of life, mostly in general health, and physical and social functioning.[61]

Box 7 Why we need a global perspective on HoFH: insights from the HICC Registry

- Poor awareness
- Underdiagnosis: lack of national cholesterol screening programmes, including universal paediatric screening for FH, and limited access to genetic testing
- Lack of systematic diagnostic criteria (genetics, variability in LDL-C levels)
- Barriers to treatment: newer therapies or LA not available or limited due to variable reimbursement
- Consideration of founder effects in certain settings

Impact on quality of life may depend on disease status and treatment, especially for patients undergoing LA given significant treatment burden affecting education and employment.[61,85,86] In contrast, a Dutch study[87] in which 90% of patients with HoFH were treated with pharmacological interventions without LA, showed that quality of life was only slightly below the national average. Transient anxiety was reported when confronted with the consequences of HoFH, such as the onset or worsening of ASCVD. Family planning delivered by a dedicated HoFH centre helped patients cope with their disease. These findings underline the importance of comprehensive support for patients with HoFH and their family in specialized lipid centres.

Global perspectives

HoFH is a major challenge as it is underdiagnosed and undertreated in every world region. As shown by the HICC Registry, the implications for cardiovascular health are depressing; the first major adverse cardiovascular event occurred at a median age of 31 years, and before 18 years in 4% of patients.[12] Treatment inequity exacerbates this; in the HICC registry, individuals in less affluent countries have higher treated LDL-C levels and experienced their first cardiovascular event about a decade earlier than those in high-income countries (mean age 24.5 vs. 37 years). Limited or no access to newer highly effective LDL-lowering therapies, and genetic testing to facilitate identification of less severe or extreme phenotypes, are important contributors (*Box 7*).[12] These findings underpin the call to action to improve HoFH care globally.[7–9]

These disparities will increase assuming the use of newer treatments continues to be restricted to more affluent countries. Changes to health policy at global and regional levels are urgently needed to ensure that all patients with HoFH receive effective treatment as soon as possible to improve cardiovascular outcome.

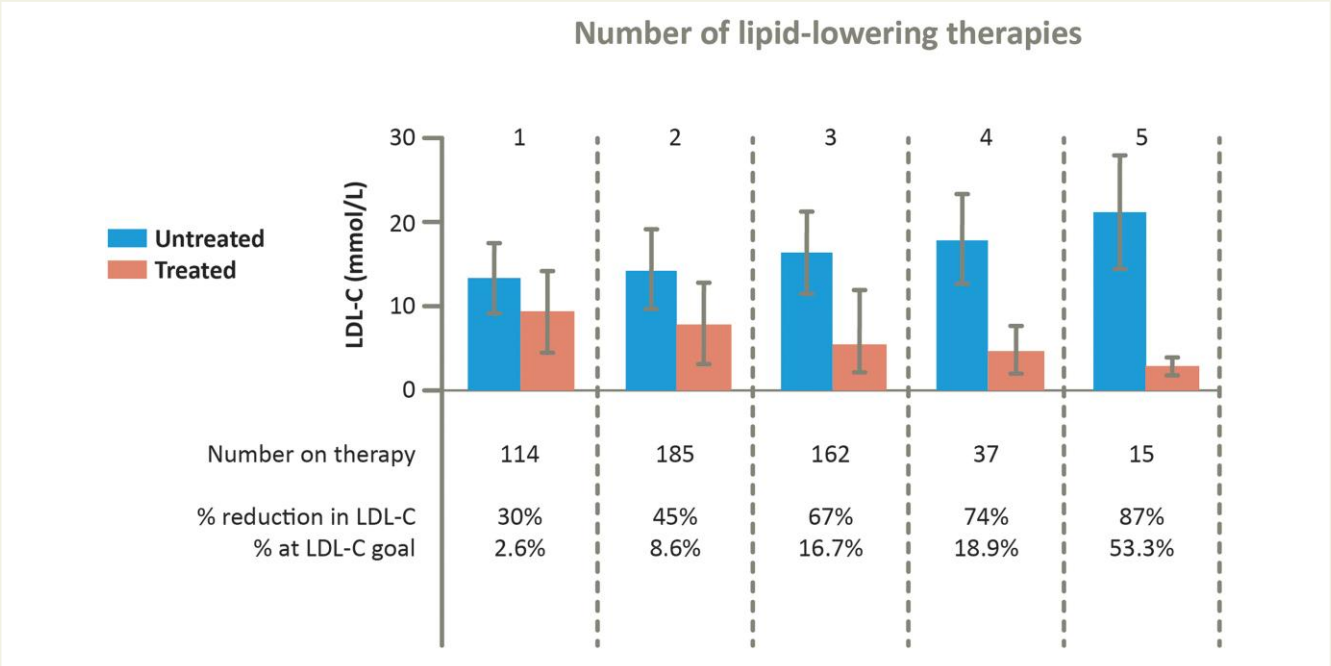

Figure 4 As shown for high-income countries in the HoFH International Clinical Collaborators registry, multidrug therapy substantially improved low-density lipoprotein cholesterol- lowering. More than 50% of the few patients on five lipid-lowering therapies attained low-density lipoprotein cholesterol goal (defined as <2.5 mmol/L in primary prevention or <1.8 mmol/L in secondary prevention). Adapted with permission from Tromp *et al.*[12]

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Key recommendations

- Creation of national screening programmes tailored to the healthcare system and culture of individual countries. These underpin the universal recommendation for early identification of HoFH via universal screening or systematic cascade screening. The panel advocates genetic testing to facilitate cascade screening; where not yet possible or privacy concerns limit implementation, screening based on LDL-C cut-offs are equally acceptable.
- Creation of education programmes to improve awareness, both among clinicians, starting from medical school, and patients.
- Creation at the local (institutional), regional, and government level of management guidelines that take account of resources, including access to specialist centres and effective lipid-lowering treatments. These should address costs associated with treatment and access to care.

Implementing clinical guidance

Systematic implementation of guideline recommendations is integral to better HoFH care, but difficult. In real world practice, lack of access to imaging and use of an adequate multi-drug therapeutic strategy are major issues (*Figure 4*). While goal attainment will likely improve with novel therapies, increasing awareness of HoFH among clinicians and improving access to imaging and treatment are paramount. New thinking on delivery of optimal management is needed, especially in less affluent countries where novel drugs are not approved or affordable and sophisticated clinical approaches may be lacking. Such approaches could include the use of telemedicine to help maintain adherence, especially during late adolescence/early adulthood,[88] web-based education, and case discussion, such as the global EAS Lipid Clinics Network,[89] together with other initiatives supported by the EAS and the International Atherosclerosis Society. Patient advocacy groups are crucial for patient empowerment, and advocating for improved care, access to new therapies, and influencing health policy.

The panel recommends a multifaceted approach including education of all stakeholders, training and upskilling of healthcare providers, creation of a multidisciplinary team, promotion of participatory medicine, creation of academic service partnerships, and provision of adequate funding of health services.[90,91] Health policy, as in Japan,[92] should focus on country-specific needs and leverage funding for what is a very rare condition with special needs, aiming to improve and sustain best care for patients with HoFH, focusing on promotion of effective detection and funding of advanced therapies. Registry data linked to patient outcomes should be used to inform health policy. Quality clinical registries should also be used as a network of collaborative centres of clinical excellence, able to provide guidance to providers.[12]

Conclusions

HoFH is still underdiagnosed and/or identified too late and remains undertreated despite its severe adverse impact on cardiovascular health (Graphical abstract). The last decade has seen much progress, particularly with new highly efficacious LDL-C-lowering therapies which offer the prospect of LDL-C goal attainment, leading to improved survival and quality of life. Yet important challenges remain. The priorities are improving education, early diagnosis, and treatment, as well as addressing inequities in access to all therapies in less affluent regions. This updated EAS consensus statement provides pragmatic guidance crucial to driving better care and improved cardiovascular health and quality of life for patients with HoFH worldwide.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Acknowledgements

European Atherosclerosis Society (EAS) Consensus Panel—Co-chairs: M.C., F.J.R., and R.A.H. The panel convened two virtual meetings; at the first meeting updates to the evidence and issues in HoFH care were discussed and the draft manuscript was discussed at the second meeting.

Author contributions

All authors contributed to the manuscript, and the complete manuscript was revised by M.C., R.A.H., F.J.R., A.L.C., and J.K.S. All panel members agreed to the conception and design, contributed to interpretation of available data, reviewed drafts, and approved the final document before submission.

Data availability

No data were generated or analysed for this manuscript.

Conflict of interest

Potential conflicts of interest outside the submitted work are summarized as follows. The following authors report participation in trials; receipt of fellowships, or grants for travel, research or staffing support; and/or personal honoraria for consultancy or lectures/speaker's bureau from: Abbott (K.A.-R., M.K., K.K.R., R.D.S., L.S.T.); Abdi-Ibrahim (M.K., L.S.T.); Acasti (D.G., R.A.H.); Ache (R.D.S.); Actelion (L.S.T.); Aegerion (M.A., E.B., D.G., M.H.-S.); Akcea (M.A., E.B., A.L.C., D.G., R.A.H., K.G.P.); Alexion Pharma France (E.B.); Alfasigma (M.A.); Amarin (M.A., M.Av., A.L.C., L.M.); Amgen (M.A., M.Av., E.B., T.F., D.G., M.H.-S., R.A.H., M.K., L.M., K.G.P., F.J.R., K.K.R., R.D.S., L.S.T., G.F.W., A.W.); Amryt (M.A., M.Av., MC, M.K., L.M., J.E.R.v.L., R.D.S., A.W.); Arrowhead (R.A.H., G.F.W.); Ascent Development (M.H.-S.); Astellas (M.H.-S.); AstraZeneca (A.L.C., D.G., M.K., K.K.R., R.D.S., G.F.W.); Bayer (M.K., L.S.T.); Biolab (R.D.S.); Boehringer Ingelheim (D.G., M.H.-S., K.K.R.); Cerenis (D.G.); CRISPR Therapeutics (K.K.R.); Daiichi-Sankyo (M.Av., E.B., A.L.C., M.H.-S., M.K., L.M., K.G.P., K.K.R., L.S.T.); Dalcor Pharma (D.G.); Danone (E.B.); Deva (M.K.); Esperion (A.L.C., D.G., K.K.R., R.D.S., G.F.W.); Gemphire (D.G.); Genfit (E.B.); Genzyme (A.L.C.); Getz Pharma (R.D.S.); GlaxoSmithKline (D.G.); HDL Therapeutics (D.G.); HLS Therapeutics (R.A.H.); Ionis Pharmaceuticals (E.B., A.L.C., D.G., M.K.); Ironwood (D.G.); Jansen (M.K.); Kowa (A.L.C., D.G., M.H.-S., K.K.R., R.D.S.); LIB Therapeutics (R.A.H., M.K., F.J.R.); Libbs (R.D.S.); Eli Lilly/Lilly (A.L.C., D.G., M.K., K.K.R.); Medpace (M.H.-S., M.K.); Menarini (A.L.C.); Merck (A.L.C., M.K., R.D.S., L.S.T.); MSD (E.B., M.H.-S., K.G.P.); Mylan (M.A., E.B., A.L.C.); Nestlé (D.G.); New Amsterdam (K.K.R.); Novartis (K.A.-R., M.A., M.Av., E.B., A.L.C., T.F., D.G., M.H.-S., R.A.H., M.K., L.M., K.G.P., K.K.R., J.E.R.v.L., F.J.R., R.D.S., L.S.T., G.F.W., A.W.); NovoNordisk (M.K., K.K.R., R.D.S., L.S.T.); Pfizer (M.A., A.L.C., D.G., R.A.H., M.K., K.K.R., R.D.S., L.S.T., G.F.W.); PTC (R.D.S.); Recordati (A.L.C., M.H.-S., M.K., L.S.T.); Regeneron (M.A., A.L.C., MC, D.G., R.A.H., K.G.P., F.J.R., K.K.R., A.W.); REGENXBIO (M.C.); Resverlogix (K.K.R.); Sandoz (A.L.C.); Sanofi (K.A.-R., M.A., A.L.C., T.F., D.G., M.H.-S., R.A.H., M.K., L.M., K.G.P., F.J.R., K.K.R., R.D.S., L.S.T., G.F.W.); Sanofi/Genzyme (M.Av.); Sanofi-Regeneron (E.B.); SCIBE Therapeutics (K.K.R.); Servier (E.B., L.M., L.S.T.); Sigma Tau (A.L.C.); Silence Therapeutics (E.B., K.G.P., K.K.R., G.F.W., A.W.); Sobi Takeda (M.Av.); The Medicine Company (D.G., M.H.-S.); Ultragenyx (R.A.H.); UniQure (D.G.); and Vaxxinity (K.K.R.). ESG Stroes reports honoraria for lectures/advisory board R.D.S. paid to his institution from Amarin, Amgen, Daiichi-Sankyo, Esperion, IONIS/Akcea, Novartis, Novo-Nordisk,

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and Sanofi-Regeneron. Manuscripts have been published in collaboration with non-academic co-authors by L.S.T. (Fitbit), and G.F.W. (Amgen). T.F. is supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (Programme EXCELES, ID Project No. LX22NPO5104)—Funded by the European Union—Next Generation EU. D.G. is supported by Canadian Cardiovascular Research Network and the Institut de cardiologie de Montréal. Equity interests are reported by K.K.R. (Cargene Therapeutics and Pemi31 Therapeutics) and J.K.S. (AstraZeneca and GSK). K.K.R. is President of the European Atherosclerosis Society. L.S.T. is Past-President of the European Atherosclerosis Society and an Editorial Board Member, The European Heart Journal. L.C.H. has no disclosures.

Funding

All authors declare no funding for this contribution.

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